IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

		Atty. Docket: SELA=5
In re Application of:	)	Confirmation No.: 3015
	)	
Yoram SELA	)	Examiner: Jake Minh Vu
	)	
Appln. No.: 10/500,634	)	Group Art Unit: 1618
	)	
Filed: January 24, 2005	)	Washington, D.C.
	)	
For: EXTENDED RELEASE COMPOSITIONS COMPRISING AS ACTIVE COMPOUND VENLAFAXINE HYDROCHLORIDE	)	

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window
Randolph Building, Mail Stop
401 Dulany Street
Alexandria, VA 22314

Sir:

I, the undersigned, Michael Grimshaw, hereby declare and state as follows:

I hold a Ph.D. in pharmaceutical chemistry from Queens University, Belfast, Northern Ireland. I have extensive experience as a senior pharmaceutical industry research and development and manufacturing executive and am currently a consultant with respect to drug delivery technologies and solid dosage forms. A true and correct copy of my curriculum vitae is attached hereto.

I understand that the above-identified application of Yoram SELA (the Sela application) is directed to an extended release dosage form of venlafaxine hydrochloride that permits controlled release of the venlafaxine hydrochloride over approximately a 24 hour period. Preferably, the dissolution characteristics of this extended dosage form bioequivalent to those of the venlafaxine hydrochloride dosage form sold under the proprietary name EFFEXOR XR. The dosage form of the Sela application includes venlafaxine hydrochloride coated onto an inert core, optionally in connection with a binder. A controlled release layer comprising a hydrophobic polymer, preferably mixed with a plasticizer, is then coated onto the formulation. The controlled release layer permits controlled release of the venlafaxine hydrochloride over the 24 hour period. In a preferred embodiment, the venlafaxine hydrochloride is coated with a layer of a hydrophilic polymeric or glyceryl monostearate (GMS) layer before being coated with the controlled release layer. It is further my understanding that the hydrophobic release layer preferably comprises an ammonio methacrylate copolymer, such as that sold under the trade name EUDRAGIT, hydroxypropylcellulose, ethylcellulose, such as that sold under the name ETHOCEL, or cellulose acetate.

It is my understanding that the examiner examining the Sela application considered the claims of the Sela application to all be obvious over the disclosure of EP0919236 of Eli Lilly and Co., invented by Heiligenstein (hereinafter Heiligenstein). It is my understanding that the Heiligenstein disclosure relates to a method of treatment of the psychiatric disorder known as Oppositional Defiant Disorder by administering an effective amount a norepinephrine reuptake inhibitor. Heiligenstein discloses that a preferred such inhibitor is the drug duloxetine but that venlafaxine may also be used for this purpose.

While Heiligenstein is not a formulation patent, it does disclose an example of a duloxetine enteric formulation comprising a duloxetine layer over a core bead. The duloxetine layer further includes hydroxypropylmethylcellulose. This layer is followed by a separating layer of hydroxypropylmethylcellulose, sucrose and talc, which is then coated with an enteric layer of hydroxypropylmethylcellulose acetate succinate (HPMCAS), along with triethyl citrate and talc. A finishing layer of hydroxypropylmethylcellulose, titanium dioxide and talc is then applied. Throughout, this example formulation of duloxetine is referred to as an "enteric formulation."

Those of ordinary skill in the art of drug formulation are well aware of what an "enteric formulation" is. Reference is made, for example, to the definition of "enteric-coated" in Dorland's Illustrated Medical Dictionary, 29th ed., Philadelphia, PA, W.B. Saunders Co, 2000, page 599, which reads:

> a term designating a special coating applied to tablets or capsules which prevents release and absorption of their contents until they reach the intestines.

Typically, enteric coatings prevent the release at the acidic pH condition of the stomach, but permit quick and immediate release under the pH conditions of the small intestine.

The dosage form of the Sela application is not an enteric formulation, but is what is known in the pharmaceutical formulation industry as an "extended-release formulation." In this regard, reference is made to page 636 of the same Dorland's Illustrated Medical Dictionary, which defines "extended-release" as:

> allowing a two-fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form.

Thus, for an enteric coated formulation (tablet or capsule), the enteric coating gets the tablets or capsules through the stomach and as soon as they get to the intestine, they are immediately released because of the pH change.

Extended-release tablets have a different mechanism of release in that release is controlled by diffusion through the coating membrane. In other words, it is not pH-dependent. Indeed, note that in the specification of the Sela application, on page 3, in the line following the table, it is explicitly stated that the dissolution characteristics are pH-independent.

Heiligenstein, at paragraph [0010], indicates that the active ingredient of the enteric layer is hydroxypropylmethylcellulose acetate succinate (HPMCAS). Those of ordinary skill in the art of drug formulation are well aware that HPMCAS is a completely distinct chemical from hydroxypropylmethylcellulose. There is no disclosure anywhere in the Sela application of the use of HPMCAS.

It is my understanding that the examiner has stated that it would have been obvious to substitute venlafaxine hydrochloride for duloxetine in the enteric coated formulation of Heiligenstein and that the differences in amounts of specific ingredients would be result-effective parameters and that it would be obvious to routinely optimize such parameters. I note, however, that a person of ordinary skill in the art seeking to substitute venlafaxine for duloxetine in the enteric formulation of Heiligenstein would optimize for optimal enteric characteristics, as this is what Heiligenstein

seeks. Completely changing the ingredients and the amounts so as to obtain a pH-independent formulation with extended-release would not be optimization of anything taught by Heiligenstein with respect to enteric coated formulations. To the contrary, it would be for a purpose which is nowhere mentioned in Heiligenstein.

It is my understanding that the laboratory of the inventor of the Sela application has actually conducted experimentation in order to make the substitutions that the examiner states is suggested by Heiligenstein and to examine the results obtained. Submitted herewith is a declaration of Dr. Yoram Sela relating to the process which was used to repeat the procedure of Heiligenstein using venlafaxine instead of duloxetine and to test the dissolution characteristics thereof in comparison with those of the products of the Sela application.

I have reviewed the results of the tests conducted as reported in the Sela declaration. It can be seen from the Figure 1 of these results that the enteric-coated formulation that one obtains when substituting venlafaxine for duloxetine provides a composition that substantially prevents the release in gastric buffer (GFS), pH 1.2, while permitting substantially total release within 1 hour in intestinal buffer

(IFS), pH 6.8. This is clearly not pH-independent and shows no extended-release characteristics whatsoever.

On the other hand, the compound made in accordance with the Sela application showed controlled release over 24 hours as seen by the Figure 2, which shows release characteristics that are independent of pH and RPM. In other words, the results at the gastric pH (1.2) are substantially identical to the results at intestinal pH (6.8). Furthermore, Figure 3 shows that the dissolution profile for the compounds of the Sela application are substantially identical and certainly bioequivalent to the release characteristics of EFFEXOR XR, which is made by a totally different process. On information and belief, EFFEXOR XR is made by a process as described in PCT application publication no. WO99/22724.

It is completely apparent to me, and one of ordinary skilled in the art would understand, that no "optimization" of the conditions of Heiligenstein would change the pH-dependent dissolution characteristics of the enteric formulation intended by Heiligenstein to the pH-independent dissolution characteristics provided by the compositions of the Sela application for the reasons explained above and as supported by the facts reported herein. It is my opinion that the formulation of the Sela application would not have been

obvious to anyone of ordinary skill in the art reading Heiligenstein.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 16th,2010 / Michael Grimshaw,Ph.D./
Date Michael Grimshaw,Ph.D.

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CAREER SUMMARY

A Senior Pharmaceutical Industry R & D and manufacturing executive with particular strengths in:

RESEARCH AND DEVELOPMENT MANAGEMENT

ANDA, Generic Products development
Drug Delivery dosage forms development
Clinical Supplies production strategies
In vivo in vitro correlations
Patent Applications – office actions – responses
"Freedom to Operate" product development

MANUFACTURING MANGEMENT

Improving production efficiencies
Cost control
Inventory management

Consultant. Drug delivery technologies.—Solid dosage forms.
[2009 March to present.]

KV Pharmaceuticals, USA
(2007 to 2009.February.)
Vice President, Strategic Design Technology and Mentoring

- Responsible for the drug delivery technologies development outside of the "prior art".
  - Focus on solid oral modified release dosage forms for both internally and externally developed products.
    - Initially, 55 internally developed products, recently re-focused to 20 projects identified as "first to file" candidates.

- Jointly responsible for the identification of new product opportunities as a member of a taskforce including an I.P. lawyer and a Director of Business Development.
  - Provided preliminary design strategies for approximately 130 candidates.

- "Freedom to operate" documentation is reviewed throughout the formulation development phase and forwarded to IP Legal prior to the pivotal biostudy.
- 10 to 12 per year reviewed and approved by IP Legal

- Responsible for the dosage form development of new delivery technologies.
  - Rapidly disintegrating tablets – 2 patents approved.
  - 3 new delivery technologies --- 2 patents approved.
  - - gastro retentive delivery system
  - - pulsatile delivery systems.

KV Pharmaceuticals, USA.
(2001 to 2007)
Vice President, Research and Development

Established a "High Performance" R&D Organization, which plays a critical role in the growth of the company:

- By recruiting, motivating and training product development scientists and managers
  - Hired 11 scientists/managers
- By acquiring processing and testing equipment
  - Established a biopharmaceutical testing lab, hired scientists (4) and purchased analytical equipment to facilitate drug characterization and development of biorelevant dissolution methods.
- By focusing on "difficult to formulate" products including highly insoluble drugs and Zero Order Drug Release Profiles – e.g., Metoprolol succinate ER tablets, Diltiazem HCl ER capsules, osmotic pump drug delivery systems
- Successfully developed 22 bioequivalent ANDA products currently being reviewed by the FDA --- 7 Paragraph IV ANDA applications
- 15 of 15 Pre-approval inspections have been completed and designated as "approvable" by the FDA
- 42 minor strengths for these ANDA products have been developed and included in the respective submissions.
- 36 "grandfather' products have been developed and launched.
- Day to day management of 32 R&D personnel

FMC Corporation, U.S.A. 1993-2001

Vice President, Research and Development
ENTEC Drug Delivery Technologies 1998-2001
Led the Division in a new strategic direction, establishing ENTEC Drug Delivery Technologies a Drug Delivery Development business, launched as a separate unit in 1998.

Completed the development studies leading to 8 patented oral drug delivery technologies.

- ENSOLV, for enhanced drug dissolution profiles leading to improved solid dosage form bioavailability.
- ENCIRC, for uniform high drug-loaded pellets.
- ENVEL, for taste masked chewable tablets.

Optimization studies included,

- Developing in vitro / in vivo correlations for oral extended-release (ER) products.
- The use of in vitro permeability and in vitro metabolism assays to help optimize formulation variables.

Development Agreements

- Signed 14 joint development agreements with large pharmaceutical, generic and venture capital companies to incorporate their active ingredient into FMC's drug delivery systems and to manufacture pilot scale GMP batches for pharmacokinetic studies.
    - Generic companies included Teva, Mylan and Andrx

Pharmaceutical Division, USA
Director, Research and Development,
(Reporting the Division Manger)
1993-1998

New excipients development

- Developed and launched fourteen new excipients for use in solid development and liquid dosage forms.
- Introduced a Portfolio Analysis process (Division Wide) to prioritize the new projects and monitor their progress through the R&D development pipeline.

Global technical services

- Refocused and expanded the level of technical services we provided to our customers. This allowed our customers to better understand how to tap into and benefit from the functionality of our excipients.
- A new technical services laboratory was set up in Brussels to better service the needs of our European customers.

Director, Development Resources,
Marion Merrell Dow Pharmaceuticals (Canada) Inc.
(Reporting the Global Director of Pharmaceutical and Analytical Sciences)
(1991-93)

PRODUCT DEVELOPMENT/CLINICAL SUPPLIES

Formulation Development

- On the Global Steering Committee during all phases in the development and launch of a **Transdermal Patch** product.
- Completed one and worked on a second Global Project to develop a new solid dosage formulation for an NCE.
- Developed eight new or improved products for the Prescription and Consumer Products Division.

Clinical Supplies

- Manufactured, packaged and labeled clinical supplies for Bioequivalence and Efficacy Studies.
- 22 studies initiated (4000 patients)
- 10 studies completed

Business Management

- Director and member of the Business Management Committee responsible for finalizing decisions affecting strategic plans, functional budgets and operational policies and procedures.

Director, Product Development and Quality Operations
Merrell-Dow Pharmaceuticals (Canada) Inc.
(Reporting to the President)
1983 - 1991

PRODUCT DEVELOPMENT / QUALITY OPERATIONS

Product Development

- Developed, scaled up and manufactured clinical supplies for eighteen new drug products. In 1990, these products contributed 19% of our total dollar sales.
- Twelve additional new products are at various stages of the product development cycle.

Process Development

- First location within Merrell - Dow to develop and scale up a totally aqueous *tablet film coating* process.

New Business Development

- Chairman of a Task Force with the mandate to review existing New Business Strategy and recommend areas for improvement.

All the recommendations were approved and implemented in the New Business Development Process.

Business Management

- Director and member of the Executive Committee responsible for finalizing decisions affecting strategic plans, annual business plans and functional budgets, acquisition / licensing of new products and operational policies and procedures.

Manager, International Quality Operations,
Merrell-Dow Pharmaceuticals Inc. (USA)
(Reporting to the Director, Global Quality Operations)
1981 - 1982

Vice President / Director of Manufacturing Services,
Richardson Merrell Canada Ltd., Richard Vicks Ltd.
(Reporting to the President)
1978 - 1981

MANUFACTURING AND MATERIALS MANAGEMENT
Member of the Executive Committee responsible for finalizing decisions affecting company policy on matters such as operations, budgeting, acquisitions and long-range planning.

Improved profitability, cut costs and increased capacity

- Implemented savings of approximately $400,000 per year by planning and coordinating company-wide efforts to reduce labor costs, material handling and distribution costs.
- Reduced inventory levels and improved turnover by 18% without sacrificing customer service levels.
- Met urgent need for 29% increase in production requirements by installing an additional (unbudgeted) high-speed liquids-filling/packaging line within 3 months.

- As plant manager, directed total operation of plant producing up to 38 million units per annum with annual sales value of $37 million, 200 employees and expense budget of $4.5 million.

- Monitored commodity market price fluctuations to time contracts with suppliers of sugar. Avoided doubling of costs in a volatile market.

- Planned and oversaw construction of a warehouse and office expansion costing $3.5 million and consisting of a 36,000 sq. ft. semi-high-rise warehouse, an 18,000 sq. ft. conventional warehouse and an 18,000 sq. ft. office/cafeteria extension.

Director, Quality Operations
Richardson Merrell Canada Ltd.
(Reporting to the President)
1974 - 1978

Quality Control Manager,
Sterling Drug Limited (Canada)
1973 - 1974

QUALITY CONTROL/QUALITY ASSURANCE

Profitability	Prevented $1 million product recall by early identification of, and response to a product quality risk. Achieved a 95% reduction in production delays resulting from laboratory inefficiencies by improving the interaction between production planning, quality control and production. Provided formulae, processing instructions, specifications, test methods and technical assistance to 4 overseas plants for the start up of manufacturing of Merrell products. Smooth start-up in each plant occurred with no out-of-stock problems.
Product Quality	As director of Quality Operations, during first year, developed a comprehensive Quality Assurance System consisting of written Standard Operating Procedures, training of operators and supervisors and auditing program covering all operations from receipt of raw materials to shipping of product. As part of the new major Corporate G.M.P. auditing program, developed 46 Minimum Standards for Manufacturing and Control for 18 manufacturing plants. Responded to new H.P.B. requirements by directing the development and use of stability-indicating assay methods within 12 months.

	Coordinated upgrading of analytical technology and efficiencies in the Q.C. laboratories in Spain, Venezuela and Mexico over 8-month period.
Cost Control	As Director of Quality Control, controlled annual budgets of $500,000 for 25 professional and technical staff. Achieved 50% cost reduction by converting to an "in-house" stability program.
Capacity Planning	For a new overseas pharmaceutical plant planned laboratory layout and equipment needs; provided quality assurance review for the entire manufacturing and warehouse facility to ensure compliance with Corporate G.M.P. standards.

Regulatory Affairs Manager,
Abbott Laboratories Limited (England)
1971 - 1973

PROFESSIONAL DEVELOPMENT

- Manufacturing Strategy and Strategic Planning HARVARD BUSINESS SCHOOL
- Quality Assurance in the Pharmaceutical Industry CENTER FOR PROFESSIONAL ADVANCEMENT (N.J.)
- Competitive Strategies HARVARD BUSINESS SCHOOL, June, 1994
- Pharmacokinetics University of Wisconsin School of Pharmacy

PROFESSIONAL AFFILIATIONS

- American Association of Pharmaceutical Scientists
- Controlled Release Society
- Pharmaceutical Society of Great Britain
- Canadian Pharmaceutical Association

EDUCATION

Queen's University, Belfast, N. Ireland

Ph.D. Pharmaceutical Chemistry,
Theses, "The Synthesis of Some Mono and Diazasteroids With Special Consideration of Their Biological Activity"

B.Sc. (Hon.) Pharmacy,
MPS Member of the Pharmaceutical Society of Great Britain

PATENTS

1.Rapidly disintegrable tablets --- Grimshaw, et al.
US Patent 7,425,341
Issued on September 16, 2008

2.Rapidly disintegrable tablets --- Grimshaw, et al.
US Patent 7,282,217
Issued on October 16, 2007

3. Microcrystalline cellulose cushioning granules --- Vladyka, Jr., et al.
US Patent 6,858,725
Issued on February 22, 2005

4 Hydrolyzed cellulose granulations of salts of drugs --- Erkoboni, et al.
US Patent 6,597,312
Issued on July 22, 2003

5 Aqueous solubility pharmaceutical formulations --- Vladyka, Jr., et al.
US Patent 6,511,681
Issued on January 28, 2003

6 Aqueous solubility pharmaceutical formulations --- Vladyka, Jr.,et al.
US Patent 6,497,905
Issued on December 24, 2002

7 Method of making granular pharmaceutical vehicle --- Vladyka, Jr., et al.
US Patent 6,379,707
Issued on April 30, 2002

8 Hydrolyzed cellulose granulations for pharmaceuticals --- Karetny, et al.
US Patent 5,858,409
Issued on January 12, 1999

9 Microcrystalline cellulose spheronization composition --- Erkoboni, et al.
US Patent 5,725,886
Issued on March 10, 1998

10 Readily available konjac glucomannan as a sustained release excipient --- King, et al.
US Patent 5,486,364
Issued on January 23, 1996

Patents 3-10 above, were originally developed as drug delivery technology systems by Entec Drug Delivery Technologies, a division of FMC Corporation.